Imatinib Mesylate for Melanoma: Will a New Target be Revealed?

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There are two general paradigms for clinical drug development. The first involves understanding a mechanism or pathway leading to disease, identifying a target, screening candidate drugs for target interaction, and then assessing efficacy in animal models and ultimately in clinical trials. This sequential process is time-consuming and expensive—successful development of a new drug can take decades and cost as much as $800 million (DiMasi *et al*, 2003). Nevertheless, this approach has led to the development of many successful drugs, such as those now used to treat many patients with hypertension and hyperlipidemia. A second, increasingly more common paradigm involves the unapproved (off-label) use of a drug developed for a different disease, such as use of imiquimod (initially developed to treat genital warts) for actinic keratoses and keloids. In some cases, an approved drug given to patients for one disease is serendipitously noted to improve a second condition in those patients, revealing a new target for drug action or a similar target in another disease. Another example is etanercept, which was initially used to treat rheumatoid and psoriatic arthritis, and later found to be effective in psoriasis (Goffe and Cather, 2003). This pathway to drug discovery, although unpredictable, is usually much quicker, since mechanistic studies and extensive screening of compounds have been bypassed.

Imatinib mesylate (Gleevec, formerly known as STI571) is a drug that has taken both paths. It was originally developed by Novartis Pharmaceuticals as a specific inhibitor of the BCR-ABL tyrosine kinase, which arises from an acquired t(9;22) genetic translocation (Philadelphia chromosome) that causes chronic myelogenous leukemia. The constitutive tyrosine kinase activity drives proliferation of malignant cells and is sufficient to induce the disease (Daley *et al*, 1990). Imatinib mesylate competes for the ATP-binding site on BCR-ABL, disabling its kinase activity, and produces a complete hematologic response in most patients (Druker *et al*, 2001). Inhibition of additional protein tyrosine kinases (PTK), c-kit, and the platelet-derived growth factor (PDGF) receptor was also noted. Gastrointestinal stromal tumors often express mutated forms of c-kit, and patients with these tumors were also found to respond to imatinib mesylate (van Oosterom *et al*, 2001). When imatinib mesylate was found effective in patients with the hypereosinophilic syndrome (Gleich *et al*, 2002), investigation into the genetic basis of this disease revealed that many of these patients, as well as some with systemic mastocytosis, harbor a chromosomal deletion that gives rise to an oncogenic fusion protein (FIP1L1-PDGFRA) involving the PDGF receptor (Cools *et al*, 2004). Imatinib mesylate is thus now considered a first-line agent for many malignancies characterized by aberrant PTK signaling via ABL, c-kit, and PDGF receptor.

We desperately need new agents to treat patients with advanced melanoma, and there is currently considerable interest in imatinib mesylate. There are several reasons to think that this drug may have therapeutic potential in melanoma. First, it is known that PTK signaling is critical for sustaining melanocyte proliferation *in vitro* and for migration of melanocytic cells *in vivo* (Halaban, 2000). Binding of ligands such as stem cell factor, hepatocyte growth factor, and fibroblast growth factor to their cognate PTK receptors on melanocytes triggers a phosphorylation cascade (mitogen-activated protein kinase pathway) that in turn activates additional kinases (PI3 and Akt) that promote cell proliferation and survival. In addition, overexpression of some PTK receptor ligands such as hepatocyte growth factor is associated with increased susceptibility to melanoma in mice (Noonan *et al*, 2001). All three known targets of imatinib mesylate (ABL, c-kit, PDGF receptor) are generally expressed in melanoma, although c-kit expression tends to be diminished in metastatic lesions (Shen *et al*, 2003).

Imatinib mesylate is currently being tested in patients with metastatic melanoma, but preliminary results of Phase II trials have not been very impressive. One trial involving 26 patients from Vanderbilt-Ingram Cancer Center and Beth Israel Deaconess Medical Center did not produce any clinical responses, but the course of treatment was limited in most patients by drug toxicity.[1] Data on expression of known drug targets in tumors was not reported. A second trial from MD Anderson Cancer Center was limited to 21 patients with biopsies demonstrating expression of relevant PTK in over 25% of tumor cells.[2] A near complete response was seen in one patient with the strongest expression of c-kit, but the remaining 20 patients experienced progressive disease over 6–12 wk.[1]

There has been a concurrent effort in several laboratories to evaluate imatinib mesylate in mouse models of localized melanoma. In a recent issue of the Journal, McGary *et al* (2004) employed a xenograft model in which human

Abbreviations: PDGF, platelet-derived growth factor; PTK, protein tyrosine kinase

[1]Eton O, Billings L, Kim K, *et al*: Phase II trial of imatinib mesylate (STI-571) in metastatic melanoma. Proc Am Soc Clin Oncol 23:713, 2004.

[2]Wyman K, Atkins M, Hubbard F, *et al*: A phase II trial of imatinib mesylate at 800 mg daily in metastatic melanoma: Lack of clinical efficacy with significant toxicity. Proc Am Soc Clin Oncol 22:713, 2003.

melanoma cells were implanted into immunodeficient mice to form subcutaneous tumors. Two melanoma cell lines were used: one line (A375SM) with strong expression of PDGF receptor-α, weak expression of PDGF receptor-β, and no expression of c-kit; and another (MeWo) with weak expression of PDGF receptor-α, strong expression of PDGF receptor-β and positive expression of c-kit. Following injection of melanoma cells, mice received phosphate-buffered saline or imatinib mesylate (100 mg per kg oral gavage three times weekly). There was not a significant difference in tumor growth (for either cell line) in mice that had received drug *versus* the saline control. To confirm tumor delivery and biological activity of the imatinib mesylate, the authors demonstrated reduced PDGF receptor phosphorylation in tumors from animals that received the drug. Potential effects of the drug on cultured cells were not examined.

In contrast to these results, Redondo *et al* (2004) in this issue of the Journal use mouse (B16F10) melanoma cells to establish subcutaneous tumors in syngeneic mice, and report that imatinib mesylate inhibits tumor growth. Mice were injected with B16F10 cells and simultaneously received intraperitoneal injections of saline or imatinib mesylate (37.5 mg per kg on 5 consecutive days per week for 2 wk). There was a 77% reduction in tumor growth in animals receiving drug compared with saline control. The results approached, but did not achieve, statistical significance ($p = 0.1$), likely due to the small numbers of animals used in the study. The authors also demonstrate that addition of imatinib mesylate to B16F10 cells in culture led to decreased proliferation that was associated with a G1/S phase arrest but not apoptosis. They were unable to detect c-kit expression in cultured B16F10 cells or tumors, and did not assess expression of ABL or PDGF receptor or their phosphorylation status.

There are several potential explanations to account for the different activity of imatinib mesylate reported by these two groups. First, imatinib mesylate could indeed have a limited spectrum of activity—for B16F10 murine cells but not A375SM, MeWo, or other human melanoma cells. Conceivably this drug, although developed against human PTK, may target a molecule selectively expressed on these murine melanoma cells. In addition, differences in drug metabolism and transport in and out of the cells could dramatically affect therapeutic responses. A second issue may relate to its absorption and bioavailability in each study. Although McGary *et al* administered the drug by oral gavage, Redondo *et al* used intraperitoneal injection. Although McGary *et al* achieved sufficient tumor delivery to downregulate PDGF receptor phosphorylation, orally administered drug may result in lower drug levels in blood and tumor compared with the intraperitoneal route. Third, there may be a role for a host immune response in the inhibition of tumor growth mediated by imatinib mesylate. In the B16F10 model used by Redondo *et al*, the tumors are syngeneic and the mice have a competent immune system, whereas in the prior study by McGary *et al*, the tumors are xenografts in immunodeficient mice. It is possible that an immune response may facilitate drug-induced tumor inhibition, although induction of specific tumor cell immunity seems unlikely given the short-term course of experiments by Redondo *et al*.

Multiple additional experiments need to be performed to resolve these issues and to further clarify the potential therapeutic effect of imatinib mesylate on melanoma in animal models. Additional human melanoma lines should be examined in the xenograft model, using intraperitoneal drug delivery. Effects on established tumors can be studied by delaying administration of the drug until tumors have formed. Tumors responding to drug should be examined histologically to ascertain effects on proliferation and apoptosis *in vivo*, as well as the presence and nature of a host inflammatory response. If positive effects on established tumors can be demonstrated, it would also be interesting to examine whether the drug can protect against tumor cell metastasis and animal survival. Should imatinib mesylate prove to be a cytostatic agent, as suggested by the results of Redondo *et al* showing a proliferation block but not induction of apoptosis, it would be worthwhile to investigate whether its efficacy can be enhanced by combination with an adjuvant such as a cytotoxic drug or proteosome inhibitor.

Preliminary results of Phase II trials in metastatic melanoma (Wyman *et al*, 2003; Eton *et al*, 2004),[2] as noted above, have not been encouraging. Should addition of another agent enhance efficacy in one of the mouse models, then such combination therapy might be worth pursuing in a clinical trial. If imatinib mesylate does prove to have activity on melanoma cells as the report by Redondo *et al* may suggest, it could still be useful as an adjuvant therapy in patients with high-risk localized disease. These animal studies suggest that c-kit and PDGF receptor are unlikely to be relevant targets, given the absence of c-kit in B16F10 cells and the lack of response to PDGF receptor dephosphorylation (McGary *et al*, 2004). The initial target for which the drug was developed, ABL, was not examined in these studies but remains a possibility given its broad expression in human melanomas (Shen *et al*, 2003). Given the highly conserved enzymatic site in many PTK, and the presence of hundreds of distinct PTK in cells, it seems plausible that other candidate targets exist. In fact, expression of several PTK has been demonstrated in melanoma lines from different stages of tumor progression but not in normal melanocytes (Easty *et al*, 1995). Of note, the related PTK inhibitor gefitinib initially appeared to benefit only 10% of patients with lung cancer, but is now recognized to be particularly effective in patients bearing particular mutations in epidermal growth factor receptor (Lynch *et al*, 2004). It is possible that a putative target of imatinib mesylate in melanoma might similarly be expressed only on a subset of tumors. If such a target can be defined in animal models, then conceivably those patients with tumor expression of the target could be identified as prime candidates for a future clinical trial.

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